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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/799,372	03/12/2004	Jeffrey S. Mumm	15060-58	7301
69949 7590 05/16/2007 PATRICK W. RASCHE (15060) ARMSTRONG TEASDALE, LLP ONE METROPOLITAN SQUARE SUITE 2600 SAINT LOUIS, MO 63102-2740			EXAMINER BERTOGGIO, VALARIE E	
			ART UNIT 1632	PAPER NUMBER
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**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

# Office Action Summary

Application No.

10/799,372

Applicant(s)

MUMM ET AL.

Examiner

Valarie Bertoglio

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-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

## Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

## Status

- 1) ☒ Responsive to communication(s) filed on 05 March 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

- 4) ☒ Claim(s) 13-18 and 31-42 is/are pending in the application.
- 4a) Of the above claim(s) 13-18 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 31-42 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☒ The drawing(s) filed on 12 March 2004 is/are: a) ☒ accepted or b) ☐ objected to by the Examiner.  
Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

## Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
- ☐ Certified copies of the priority documents have been received.
  - ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  - ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

## Attachment(s)

- |  |   |
|--|---|
| 1) <input type="checkbox"/> Notice of References Cited (PTO-892)   | 4) <input type="checkbox"/> Interview Summary (PTO-413)<br>Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)                                   | 5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)             |
| 3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08)<br>Paper No(s)/Mail Date _____ | 6) <input type="checkbox"/> Other: _____  |

### **DETAILED ACTION**

Applicant's reply dated 03/05/2007 has been received. Claims 1-12 and 19-30 are cancelled. Claims 13-18 are withdrawn as being drawn to a non-elected invention. Claims 31-42 have been added. Claims 13-18 and 31-42 are pending and claims 31-42 are under consideration in the instant office action.

#### ***Specification***

The previous objection to the disclosure is withdrawn in light of Applicant's amendment to the specification.

#### ***Claim Objections***

The objection to claim 30 is withdrawn in light of Applicant's cancellation of the claims.

Claim 33 is awkward in the use of the phrase "being from the species that is the transgenic fish". The phrase would retain its intended meaning but be more precisely worded as "being from the same species as that of the transgenic fish".

Claim 34 is awkward in the use of the phrase "being from a species other than the transgenic fish". The phrase would retain its intended meaning but be more precisely worded as "being from a species that differs from that of the transgenic fish".

#### ***Claim Rejections - 35 USC § 112-1<sup>st</sup> paragraph***

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

#### ***Written Description***

The rejection of claim 25 is maintained as it relates to newly added claims 38-40 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s)

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contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The rejection is maintained for reasons of record set forth at pages 3-4 of the office action dated 12/13/2006. Applicant does not appear to have addressed this rejection specifically other than to state the claim 25 has been cancelled. In general, at page 8 of Applicant's Remarks, it is noted that screening DNA sequences for those that confer tissue and cell type specific expression is routine in the art.

However, in response, while the technology of isolating or determining regulatory regions may be routine in its general protocols and methods, not only would such experimentation require experimentation outside the scope of the claimed invention, but any routine nature of such experimentation fails to overcome the lack of descriptive support for such elements in the instant specification.

Applicant is reminded that the claims lack written description because in the instant case regulatory DNA sequences that drive specific expression to skeletal, cardiac, bone or cartilage cells of a medaka or zebrafish encompassed by the claims is not described. Applicant is claiming a cell wherein the critical element of the invention is a promoter driving gene expression to skeletal, cardiac, bone or cartilage cells. The specification describes a number of tissue-specific regulatory sequences but fails to describe that encompassed by claims 26-28.

#### *Enablement*

The following new grounds of rejection is necessitated by amendment.

Claims 31-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a transgenic zebrafish and medaka whose genome comprises a transgene encoding an ablation-promoting moiety and/or a reporter moiety operably linked to a promoter and/or enhancer

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wherein the transgene is expressed in a reproducible spatial and temporal pattern and is inherited through the germline of the fish and for a transgenic zebrafish or medaka fish whose genome comprises a transgene encoding an ablation promoting moiety operably linked to an upstream activating sequence and a minimal promoter wherein a transcriptional activator that binds the upstream activating sequence regulates the expression of the transgene, does not reasonably provide enablement for use of any regulatory DNA sequence such as an enhancer without at least a minimal promoter. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Enablement is considered in view of the Wands factors (MPEP 2164.01(a)). The court in Wands states: "Enablement is not precluded by the necessity for some experimentation such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue,' not 'experimentation.' " (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations." (*Wands*, 8 USPQ2d 1404). The factors to be considered in determining whether undue experimentation is required include: (1) the quantity of experimentation necessary, (2) the amount or direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims. While all of these factors are considered, a sufficient amount for a *prima facie* case are discussed below.

The newly added claims are drawn to use of any regulatory DNA sequences, including transcriptional repressors as well as an enhancer without the presence of a minimal promoter.

The specification teaches making transgenic zebrafish using a Gal4-UAS system comprising separate constructs comprising a GAL4 encoding gene operably linked to the goldfish  $\alpha$ -l-tubulin promoter, DsRed operably linked to a UAS and CFP-nitroreductase operably linked to a UAS. The resulting fish express DsRed and CFP-nitroreductase in neural cells (pages 67-68, paragraph [000243]). Upon exposure to metronidazole, nitroreductase expressing cells were eliminated. The specification also teaches making germline transgenic zebrafish using a gene encoding GFP-nitroreductase fused to a Fugu ChAT promoter (paragraph [000249] and [000262]). The specification also teaches a system comprising transgenic zebrafish transiently transfected with CFP-nitroreductase operably linked to a carp  $\beta$ -actin core promoter and 14 UAS repeats. A GAL4NP16 driver (paragraphs [00257-000258]) can be introduced to direct gene expression wherein GAL4/VP16 is operably linked to a promoter. The specification specifically teaches an  $\alpha$ -l-tubulin-Gal4-VP16 driver.

The newly added claims, as written, fail to require the presence of a minimal promoter and merely require the presence of either a generic regulatory sequence or a UAS. Thus, the claims encompass use of repressor and enhancer elements without at least a minimal promoter, which is necessary to initiate transcription. DNA regulatory sequences without a promoter fail to provide the necessary function to drive expression as required by the claims. Without such expression, one of skill in the art would not know how to use the invention.

Claim 41 is wholly unclear as set forth below under 112-2<sup>nd</sup> paragraph. However, it appears that the claim fails to require expression of the transgene encoding an ablation-promoting moiety. Claim 41 mentions that the transcriptional activator is required for expression of the encoded transgene product but it fails to either require that it be capable of regulating expression or to actually require this expression. The presence of the transgene without expression would result in a fish without a patentable use and is therefore not enabled. The claims should require that the transcriptional activator be capable of regulating expression of the transgene.

***Claim Rejections - 35 USC § 112-2<sup>nd</sup> paragraph***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

The previous rejection of claims 19-30 under 35 USC 112, 2<sup>nd</sup> paragraph is withdrawn in light of Applicant's cancellation of the claims.

Claims 35,37 and 41-42 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 35 is unclear as written. Claim 35 is not clear because it depends from claim 31, which requires a regulatory DNA sequence be present. Claim 35 required that the transgene be inserted such that an endogenous regulatory DNA sequence regulates expression of the transgene. Thus, claim 35 is not consistent with claim 31. It is not clear whether 2 regulatory sequences are required or if that of claim 35 replaces that of claim 31.

Claim 37 is unclear because it depends from claim 31 but refers to “a transgene” rather than “the transgene”, making it unclear whether claim 37 is referring to the transgene of claim 31 or to a different transgene.

Claim 41 is wholly unclear as a result of the use of dashes. It is not clearly delineated how the structure of the claim is to flow and cannot not be determined what is intended. It is not known if the “also encoded” is referring to the transcriptional activator. Furthermore, the phrase “being also encoded by the transgene that encodes the ablation promoting moiety” is unclear because it is not known whether the transcriptional activator is the ablation promotion moiety or whether the “transgene” of the claim is a nucleic acid comprising two separate transgenes, one encoding a transcriptional activator operably linked

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to its own promoter and a second transgene encoding an ablation promoting moiety operably linked to its own promoter. Claim 42 depends from claim 41.



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*Conclusion*

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Valarie Bertoglio whose telephone number is (571) 272-0725. The examiner can normally be reached on Mon-Thurs 5:30-4:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272-4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).



Valarie Bertoglio  
Primary Examiner  
Art Unit 1632